REMARKS

Claims 1 and 23 have been amended to more clearly define that which applicants believe to be their invention and to address the various 35 USC 112 objections the Examiner has raised as detailed below. The amendments to the claims do not introduce any new matter. Claim 20 is new and support for that claim is found in paragraph 0030 of the specification.

1. Claims 12, 16-17, and 19 are objected to for being in improper dependent form. More particularly, claim 12 is objected to for making reference to the pH of "said solution" wherein claim 1, from which claim 12 depends, references the pH of the "combination". Claim 1 and claim 12 have each been amended to remove the reference to a "combination" and rather simply state that the coating step is conducted at the specified pH.

Claims 16-17, and 19 are objected to because claim 15 from which they depend used the transitional language "consisting of" and the dependent claims include additional elements relative to the invention of claim 15. Claim 15 has been amended to replace the transitional language with the open transitional language "comprising". Claim 15 is further objected to by the Examiner because the claim recites 'the pH of said suspension between...". Applicants have further amended claim 15 to state that the pH of the combination is adjusted to a value between 10.0 to about 12.5.

The amendments to claims 1, 12 and 15 are believed to be fully responsive to the Examiner's objections and applicants respectfully request the withdrawal of the objections to claims 12, 16-17, and 19 for being in improper form.

2. Claims 1-3, 5, 9, 13-14 and 17-19 stand rejected under 35 USC 112, first paragraph for failure to comply with the written description. More particularly, the Examiner

contends that the specification discloses the use of the pH range of 10.5 to 12.5 only with regards to long incubation times. Applicants respectfully traverse the Examiner's statement. However, to advance the prosecution of the present application applicants have amended claim 1 to incorporate the limitation of claim 10, to state that long coating times of 1-10 days are used with the recited pH range.

The Examiner also continues reject claims 14 and 19, stating that with regards to the step of adjusting the pH of the combination, written support is only found in the context of using the specific conditions of Examples 1.2 and 1.3. Applicants respectfully traverse this rejection for the reasons stated in the previous response. However, to advance the prosecution of the present application, applicants have cancelled claim 14 and amended claim 19 rendering the rejection moot.

The Examiner has also objected to claim 2 as lacking written description support for polymerizing the protein by a chemical treatment. Again, applicants traverse this rejection and contend paragraphs 0026 and 0027 of the specification, in conjunction with common knowledge of the skilled practitioner, fully support the previously submitted amendments to claim 2. However, to advance the prosecution of the application claim 2 has been amended to state the protein is a polymerized protein, and similarly, claim 19 is amended to state that the protein is polymerized strepavidin. Support for those amendments is found in paragraphs 0026 and 0027 of the specification.

The Examiner has also objected to new claim 17 as not meeting the written description requirement for the recitation of the range "about 0.3 to about 1.5 M". As applicants have noted, the specification states at paragraph 0031 that one embodiment of the invention uses a range of 0.3 to 1.5 M. The Examiner contends that recitation of a range of "0.3 to 1.5 M" fails to support a range of "about 0.3 to about 1.5 M." Similarly, the Examiner has objected to the use of the transitional language "consisting essentially of" and the

statement "about 88%" in claim 18 as not being supported by the specification. Applicants respectfully traverse these rejections and note that there is no in haec verba support requirement for complying with 35 USC 112, first paragraph.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117. As the Federal Circuit has held, one of ordinary skill in the art would understand that use of the term "about" is intended to encompass the range of experimental error that occurs in any measurement. See *BJ Services Co. v. Haliburton Energy Services Inc.*, Fed. Cir, 338 F3d 1368 (2003). Similarly the transition phrase "consisting essentially of" is an art recognized phrase that allows a claim to be open to unlisted ingredients that do not materially affect the basic and novel properties of the invention (e.g., impurities that cannot be completely eliminated; see e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997)).

The use of the terms "about" and "consisting essentially of" is accepted under US patent law, particularly in the field of biotechnology, to designate that applicants are not bound by exact numbers, or the possibility of impurities. The amendments of the claims to include these terms/phrases does not substantially increase the scope of the claims, and one of ordinary skill in the art would readily appreciated that as of the filing date of the application, applicants were in possession of the invention as now claimed disclosed. Applicants respectfully submit that claims 17 and 18 as previously submitted fully comply with the written description requirement of 35 USC 112, first paragraph.

Claims 1-3, 5, 9, 13-14 and 17-19, as amended herein are believed to fully comply with the written description requirement of 35 USC 112, first paragraph. Accordingly, applicants respectfully request the withdrawal of the rejections under that statutory section.

3. Claims 1-3, 5 and 9-19 stand rejected as being indefinite. More particularly the Examiner has objected to the use of the phrase "strongly alkaline conditions". Claims 1 and 15 have been amended to remove the objected terminology, rendering the rejection moot.

4. Claims 15 and 17 stand rejected as being anticipated by Vaynberg in light of Bocquier and Bohidar. Claim 15 has been amended to specify that the pH of the combination is adjusted to a value between 10.0 to about 12.5 and the combination is incubated for 1 to 10 days in the absence of a crosslinking agent. Support for the amendment is found in original claim 1, and paragraphs 0015, 0025 and 0030. The cited references fail to teach the recited pH range and an incubation time. Accordingly, applicants respectfully submit that the cited references fail to anticipate the claim as amended and respectfully request the withdrawal of the rejection of claims 15 and 17 as being anticipated by Vaynberg in light of Bocquier and Bohidar.

5. Claims 1-2, 13, 15 and 17 stand rejected as being anticipated by Lou et al in view of Rossjohn et al. and Weis et al. Applicants respectfully traverse this rejection.

Lou et al. discloses a method of adsorbing a protein (streptolysin-O) onto a polystyrene latex particle. However, Lou also teaches that a crosslinking agent (carbodiimide) must be used to obtain a stable composition. As stated in the first sentence of the Detailed Description:

> A significant feature of the present invention is embodied in a complex consisting of polystyrene latex particles adsorbed with streptolysin-O antigen in an alkaline environment, the adsorption occurring in the presence of carbodiimide. (emphasis added)

The application repeatedly states the importance of crosslinking the adsorbed proteins to stabilize the final product (see column 4, lines 34-48). Thus Lou et al teach away from the present invention which provides a method for producing a stable coated microparticle in the absence of such a crosslinking step. To clarify this distinguishing characteristic of the present invention, applicants have amended claim 1 to use the closed transitional language "consisting of", and have amended claim 15 to specifically exclude the use of such crosslinking agents in the claimed method. Lou et al. fails to teach or suggest that a stable composition can be formed by adsorbing proteins onto a polystyrene microparticle in the absence of a crosslinking agent.

Moreover, since Lou et al teach that such a crosslinking step is conducted "in conjunction with" the adsorption step and is necessary to achieve stability, the reference teaches away from the present invention which specifically excludes the use of such a crosslinking step. Lou et al also fails to teach or suggest the long incubation times that are used in applicants' process to produce the stabile coated microparticles. Accordingly, applicants respectfully submit that Lou et al fails to anticipate the claims invention and applicants respectfully request the withdrawal of the rejection of claims 1-2, 13, 15 and 17 as being anticipated by the cited references.

6. Claims 1, 9 and 13 stand rejected as being obvious over Vaynberg in light of Bocquier and Bohidar. Applicants respectfully traverse this rejection.

The Vaynberg reference discloses the adsorption of a polyampholyte gelatin onto colloidal matrices, including polystyrene, and the effect of various parameters on gelatin adsorption. However, Vaynberg fails to teach or suggest the high alkaline pH and long incubation times that applicants have used, and now claim as their invention, that produce the surprisingly stable protein adsorbed microparticles. The Vaynberg article focuses on

conditions that maximize the loading of gelatin on the various particles but fails to provide any information regarding the stability of their compositions. There is no data presented or any discussion regarding conditions that will reduce bleeding from the formed compositions. Accordingly, Vaynberg fails to provide any direction to one skilled in the art with regards to a procedure that optimizes the stability of microparticles that comprise adsorbed proteins.

Applicants have discovered that incubating the microparticles and the protein at an alkaline pH for long periods of time (1 to 10 days) produces optimally stabilized compositions. Vaynberg provides no such information or any suggestion that would direct one to use such long incubation times at pH of 10 to 12.5.

First of all, Vaynberg explicitly teaches that the maximum adsorption of gelatin is obtained at around pH 6.2 for coating of polystyrene particles (p. 469, left column, lines 5-7). This value is far removed from the highly alkaline (pH 10-12.5) levels used in the claimed invention and the reference provides no teaching or suggestion that increasing the pH would have any impact with regards to adsorption of proteins. The Examiner contends that applicants have taken this statement out of context and that other sections of the reference state that pH differences were "not critical" and "produced little variation" in the adsorption efficiency of gelatin onto the polystyrene (p. 469, right column, l. 25 to p. 470, left column and Figs. 2-3).

Applicants respectfully submit that the statement on page 469, left column, lines 5-7 speaks for itself and that the authors clearly stated "In contrast, [to the effects observed with acrylic latex] the effect of pH on gelatin adsorption to PS [polystyrene] is noticeably weaker, with a maximum around pH 6.2". This statement is clearly directed to the interactions between pH and the adsorption of a protein to a polystyrene microparticle. Regardless of more generic statements made in the reference noting that the overall impact of pH on adsorption was minimal, the authors specifically state that a maximum effect was obtained at

pH 6.2 for polystyrene microparticles. The meaning of this statement needs no further interpretation, and the surrounding text does not change the explicit meaning of the statement.

At the very least, an objective reading of Vaynberg's statement (and the surrounding text) fails to provide any motivation for one to test the effect of pH at the high alkaline range of 10 to 12.5, since changes in pH, if having any effect at all, has a maximum effect at the acidic pH of 6.2. Furthermore, applicants respectfully submit that the Vaynberg objective teaching actually discourages one from testing strong alkaline conditions as such conditions would cause a drop in absorption (however minimal that effect may be), and thus the objective teaching teaches away from applicants' invention which uses a strong alkaline pH.

The Examiner argues that it would have been obvious for one of ordinary skill in the art to employ "slightly higher pH values" through routine optimization/experimentation of the conditions of Vaynberg with a reasonable expectation of success. Applicants respectfully submit that the Examiner's characterization of applicants' pH range as "slightly higher" than those used by Vaynberg is simply inaccurate. Applicants point out that due to the logarithmic scale of pH (pH representing the logarithm of the reciprocal of hydrogen-ion concentration in gram atoms per liter), a pH of 10.5 (as required in claims 1) is 5 times more alkaline than the highest pH value (pH of 10) mentioned in Vaynberg, and thus not just "slightly" more alkaline. Applicants respectfully submit that an objective view of concentration levels would characterize a five fold difference as a substantial difference in quantity and not the insignificant/slight difference the Examiner contends it to be.

Furthermore, the only instance in which pH 10 was employed in Vaynberg's studies relates to the observed amount of swelling that occurs in the adsorbed layers as a function of pH (see Figure 8 and accompanying text). Increasing pH results enables a thicker (i.e., expanded) layer of gelatin, as a result of swelling of the gelatin polymers (p. 470, left column,

first full paragraph). Thus the use of pH 10 produces a more swollen layer, not a denser layer as claimed by the Examiner (density is typically reduced upon the swelling of materials). This induced swelling in the presence of alkaline pH is the same effect as observed for free gelatin in solution. Thus the swelling effect is unrelated to adsorption of the gelatin to the microparticle. Furthermore, Vaynberg fails to note any advantage or desirability for such a swelling, it simply represents an experimental observation. The Examiner fails to explain how an increased swollen gelatin layer (i.e., wherein the polymers have simply expanded, and have not increased in density), is desirable and how such an observation would motivate one to use even higher alkaline pHs than the highest level tested in Vaynberg. Accordingly, contrary to the Examiners' assertions the results of this experiment would impart no motivation to do what applicants have done and now claim as their invention, simply because the reported results with regards to swelling of the gelatin are unrelated microparticle adsorption.

Furthermore, the numerous other experiments that actually relate to the amount of protein adsorbed onto the microparticle relative to pH fail to test any values near pH 10. Figure 2 shows equilibrium adsorption constants on polystyrene (and acrylic latex) as a function of pH, and the highest pH shown is pH 9. Figure 3 should entropy of gelatin adsorption on polystyrene and acrylic, and again, the highest pH shown is pH 9. Figures 4 and 5 likewise only show results up to pH 9. In Figure 7, which the Examiner specifically points out, the pH's reported are 5.7, 6.6, and 8.8. Thus, arguments regarding Vaynberg's teachings should not be extrapolated beyond the pH values actually tested and reported by Vaynberg. The speculation by the Examiner on the effects of pH ranges beyond those specifically discussed by Vaynberg, in relation to adsorption of proteins on microparticles, appears to be based on impermissible hindsight gleaned from applicants' reported unexpected results.

The Examiner also contends that motivation to use alkaline pH ranges beyond those actually disclosed in the Vaynberg reference comes from "the normal desire of scientists and artisans to improve on what is generally known". Such a concept is simply too abstract to provide the motivation required to establish a prima facie case of obvious in the absence of any guidance provided by the cited reference as to what parameters to alter to gain such desired improvement.

The Examiner contends that one of ordinary skill in the art could have generated applicants' claimed invention through routine optimization/experimentation of known procedures. Applicants respectfully traverse and respectfully submit that optimization of a procedure can only occur when there is guidance as to what parameters should be varied to produce the optimal result. There is simply no teaching in Vaynberg that varying the pH and extending incubation times would lead to an optimized method of preparing stabilized protein adsorbed microparticles. Obvious to try is not the proper standard for patentability. While it may be obvious to alter all parameters that are known to impact adsorption of proteins (i.e. ionic concentration, pH, temperature, crosslining agents...) until arriving at applicants invention, the prior art must provide some indication of which parameters are critical, or which of the possible choices would lead to success. An obvious to try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co. 902 f.2d 943(Fed. Cir. 1990). The cited references provide no guidance for selecting the specific parameters of pH and length of incubation for modification as applicants have done to create a process for producing surprisingly stable protein adsorbed microparticles.

The secondary Bocquier and Bohidar references are cited as evidentiary references teaching the inherent properties of the protein (gelatin) used in the Vaynberg reference. Accordingly, these references fail supplement the inadequacies of the Vaynberg reference with regards to conditions used to stably adsorb proteins onto a microparticle. Therefore, for the reasons stated above, applicants respectfully submit claims 1, 9 and 13 are patentable over the teachings of Vaynberg in light of Bocquier and Bohidar, and applicants respectfully request the withdrawal of the rejection of those claim for obviousness.

7. Claim 2 stands rejected as being obvious over Vaynberg in light of Bocquier and Bohidar and in view of Tischer et al. Claim 3 stands rejected as being obvious over Vaynberg in light of Bocquier and Bohidar and in view of Desai et al. Applicants respectfully traverse these rejections.

The inadequacies of the Vaynberg reference in combination with Bocquier and Bohidar with regards to conditions used to adsorb proteins onto microparticles has been discussed above. The cited additional secondary references, Tischer et al and Desai et al, are directed to the treatment of proteins before they are adsorbed onto particles. Accordingly, the cited Tischer et al and Desai et al references fail to supplement the inadequacies of the primary reference with regards to the pH range and the long incubation times recited as limitations of claim 1. Since claims 2 and 3 depend from claim 1, claims 2 and 3 are believed patentable over the cited combination of references. Accordingly, applicants respectfully request the withdrawal of the rejection of claim 2 and 3 for obviousness over those references.

8. Claims 10-12 and 16 stand rejected as being obvious over Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al. in view of Ryan et al.

The inadequacies of the Vaynberg and Lou references have been discussed above. The Examiner has cited Ryan for its teaching that the adsorption of proteins onto polystyrene is affected by parameters such as pH, ionic strength, and period of incubation (column 14, lines 42-55). No further details regarding these parameters are provided by Ryan. The Examiner concludes that it would have been obvious to optimize the incubation time based on the teaching of Ryan, even though Ryan fails to teach any specific incubation time or desirable ranges of time.

Applicants respectfully submit that Ryan at best can only represent an invitation to experiment. The Examiner has failed to provide any rationale of why one reading the Ryan disclosure would select incubation time as the parameter to vary when Ryan lists several different parameters that can be varied to "accomplish" binding of the protein to polystyrene. Furthermore, Ryan fails to provide any specific example or embodiment or illustration of what lengths of incubation times should be investigated. None of the cited references teach or suggest the long incubations times that are required by applicants claimed method. Nor is there any teaching or suggestion of conducting the adsorption reaction under a high alkaline pH and for long incubation times. Given the total lack of direction provided by the cited references applicants can only conclude that the Examiner is relying on impermissible hindsight to conclude that "routine experimentation" would lead one of ordinary skill in the art to select the specific parameters that applicants have modified and to modify them in the manner that applicants have and now claim as their invention.

A mere reference to skilled practitioners' desire to improve upon what was done before provides insufficient guidance to prepare the novel method of the present invention.

The cited references for all their combined teachings failed to teach or suggest that the use of a pH of 10-12.5 in conjunction with long incubation times of 1 to 10 days would produce a superior product. This surprising result was discovered by applicants and is not suggested in any of the cited references. Accordingly, claims 10-12 and 16 are believed to be patentable over the combined teachings of Vaynberg in light of Bocquier and Bohidar in view of Ryan et al., as well as the combined teachings of Lou et al in view of Rossjohn et al. and Weis et al. in view of Ryan et al. The withdrawal of these rejections is respectfully requested.

9. Claims 10-12, 14, 16 and 18-19 stand rejected as being obvious over Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al. in view of Schmid.

Applicants note that the Schmid reference is in German and applicants were not provided a copy of the translation that the Examiner relied upon for the basis of her rejection. Applicants have had insufficient time to acquire a complete translation of the Schmid reference and therefore to a large extent are relying on the Examiner's characterization of the teachings of that reference. However, applicants have obtained a translation of the sections identified by the Examiner. Schmid discloses that while the coating step may be performed for 0-50 hours, it is preferable to conduct the coating step for up to 20 hours and most preferred to conduct such a step for 1 -20 hours. The Examiner, in referencing column 4, lines 5-25 of Schmid contends that the reference discloses that incubation time is important for the effectiveness of the method. However, applicants note that column 4, lines 5-25 relates to the separation of weakly bound or non-bound proteins form particles after an initial adsorption step, and thus the referenced paragraph is unrelated to the coating step itself. On the contrary, the Schmid reference teaches that the mere adsorption step is not sufficient to

obtain the desired coating results, and that a UV-irradiation step is absolutely necessary to achieve the desired coating of the microparticles.

Schmid teaches the inclusion of procedural steps such as heating and UV crosslinking that are excluded in applicants' claimed invention. Moreover Schmid also fails to teach or suggest the adsorption of a protein to polystyrene microparticles under strong alkaline conditions (e.g., pH of 10-12.5) for an extended period of time (e.g., 1-10 days or 4-7 days). Furthermore, since the method disclosed in Schmid utilizes additional steps that substantially distinguish that method from the present invention, one cannot simply select one of the parameters disclosed in Schmid and apply that one parameter change to the Vaynberg teaching to generate the same result as reported by the entirety of the Schmid procedure. Schmid teaches that the UV treatment is important to achieve their reported results. It remains unclear what impact the incubation time of the adsorption step had on the final properties of the formed product. Furthermore, Schmid states a preference for shorter incubations times of 20 hours or less thus teaching away from the use of long incubation times of 1-10 days as applicants now claim.

Applicants have described a simple procedure for obtaining stabilized microparticles in the absence of a crosslinking step. Alternatively, applicants have discovered that long incubation times a strong alkaline pH provides a stably adsorbed proteins on polystyrene microparticles. Absent applicants disclosure there is no motivation for picking and choosing the various elements from the various cited references as the Examiner has done in an attempt to reconstitute applicants' invention. There is simply insufficient guidance provided by the combined teachings of the cited references that would lead one to the present invention. Nor is there any teaching that would suggest stable protein adsorbed microparticle compositions could be formed in the absence of a crosslinking step.

Accordingly, claims 10-12, 14, 16 and 18-19 are believed to be patentable over the combined teachings of Vaynberg in light of Bocquier and Bohidar in view of Ryan et al., as well as the combined teachings of Lou et al in view of Rossjohn et al. and Weis et al., in view of Schmid (DE 199 24 643). The withdrawal of these rejections is respectfully requested.

10. Claim 5 stands rejected as being obvious over Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al. in view of Bangs. Applicants respectfully traverse this rejection.

The inadequacies of the teachings of Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al. have been previously address above with regards to the adsorption of proteins on polystyrene microparticles. The Bangs reference is cited in support of the Examiner's position that microparticles having magnetizable cores were known at the time of applicants' invention. Bangs fails to provide any further guidance with regards to adsorbing proteins onto microparticles. Accordingly, claim 5 is believed to be patentable for the same reasons that claim 1 is patentable over the cited Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al.teachings. Therefore, claim 5 is believed to be patentable over Vaynberg in light of Bocquier and Bohidar or alternatively Lou et al in view of Rossjohn et al. and Weis et al. in view of Bangs. The withdrawal of the rejections of claim 5 over these references is respectfully requested.

11. Claims 15-19 stand rejected as being obvious over Schmid in view of Vaynberg et al, Lou et al, and Serra et al. Applicants respectfully traverse this rejection.

The claims have been amended to specify that the process excludes heat treatments or UV irradiation. Similar to Lou, Schmid teaches crosslinking of the polymers to enhance the

stability of the final product. Applicants' unique procedure provides a stable product in the absence of such additional steps. Furthermore, the references fail to teach the very procedural steps that applicants use in their procedure to generate the stable composition. In particular, the references fail to teach or suggest incubating the reaction at a strong alkaline pH of 10-12.5 for an extended period of time (1 to 10 days).

Again, although the references suggest that altering pH, salt, and incubation times may affect adsorption rates, the references fail to provide specific guidance as to what combination of features will produce the stable constructs of the present invention. The Examiner picks and chooses various elements from the individual references and recombines them to reconstitute applicants' invention without sufficient motivation for doing so. It is improper for an Examiner to selectively pick and choose elements from the prior art to arrive at the claimed invention absent a convincing line of reasoning as to why such a selection would have been obvious. Ex parte Clapp, 227 USPQ 972 (BPAI 1985).

The Examiner has also cited the teaching of Serra et al for its generic teaching that ionic strength and pH can alter adsorption rates. Such a generic disclosure of a general list of parameters that may impact adsorption fails to provide sufficient guidance to direct one of ordinary skill to the specific combination of adsorbing proteins onto polystyrene microparticles in the presence of a high alkaline pH treatment for an extended incubation time. The Serra and Ryan references represent a mere invitation to experiment and do not make the present invention obvious.

Any improvement of an old process can be characterized as optimizing what was previously known. However, in the absence of any guidance suggesting which specific parameters to modify, and the manner in which such identified parameter should be modified, such prior knowledge is insufficient to establish the obviousness of an improved process. To hold otherwise leads to a rejection of inventions under an impermissible "obvious to try"

standard of patentability. When prior art references require a selective combination and further modification to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. It is impermissible to use the claims as a frame and the prior art references as a mosaic to piece together a facsimile of the claimed invention. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 f2d 1044 (Fed Cir 1988).

The Examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness (MPEP 2142), and applicants respectfully submit that the Examiner has failed to meet this initial burden. When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. See, e.g., *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)

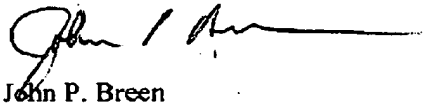
The Examiner has cited Vaynberg as providing motivation for using pH of 10 or greater, noting that gelatin layers were known to swell upon exposure to such conditions. This swelling of the polymer leads to increased thickness of the gelatin layer, but presumably decreases the density of the layer. However this swelling is completely unrelated to adsorption or bleeding rates of the formed product. In fact the Examiner has failed to cite any reason why one would be motivated to swell the adsorbed layer, and thus fails to support her

contention that one or ordinary skill would be motivated to use even higher pH ranges in a process relating to adsorbing proteins onto microparticles. The reported observation of pH induced swelling of gelatin by Vaynberg is unrelated to adsorption and thus cannot serve as motivation for formulating an improved process to adsorb proteins onto microparticles.

Applicants have discovered that a process using a strong alkaline pH and long incubation times produces a superior product. The cited references fail to teach or suggest applicants' novel combination of procedural steps that produce the surprisingly stable product. Claims 15-19 are believed to be patentable over the combined teachings of Schmid in view of Vaynberg et al, Lou et al, and Serra et al. Accordingly, applicants respectfully request the withdrawal of this rejection.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections and the claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance. If any further discussion of this matter would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



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